Journal of Surgical Oncology 1997;66:130–133

# Second Primary Carcinoma in the Residual Cervical Esophagus After Thoracic Esophagectomy: Report of Five Cases

SATOSHI MURATA, MD,[1] HOICHI KATO, MD,[1]* HIROKI TAMURA, MD,[1] YUJI TACHIMORI, MD,[1] HIROSHI WATANABE, MD,[1] HAJIME YAMAGUCHI, MD,[2] AND YUKIHIRO NAKANISHI, MD[3]

[1]*Department of Surgery, National Cancer Center Hospital and Research Institute, Tokyo, Japan*

[2]*Department of Internal Medicine, National Cancer Center Hospital and Research Institute, Tokyo, Japan*

[3]*Department of Pathology, National Cancer Center Hospital and Research Institute, Tokyo, Japan*

**Background and Objectives:** Development of second primary carcinomas after thoracic esophagectomy has become of much concern, because recently the prognosis of thoracic esophageal carcinoma after esophagectomy with extended lymph node dissection has been improving. We report our experience of diagnosing and treatment second primary carcinomas arising in the remaining esophagus after thoracic esophagectomy.

**Methods:** Among 253 patients who underwent esophagectomy for thoracic esophageal carcinoma more than 2 years previously, second primary esophageal carcinomas developed in five (2.0%), and these five patients were examined.

**Results:** All second primary carcinomas were found by endoscopy, and were diagnosed as superficial carcinoma (Tis or T1) of the residual cervical esophagus. One patient underwent laser irradiation, another endoscopic mucosal resection, two had surgical mucosectomy, and one segmental resection of the esophagus. After the second treatment, three patients were disease free for 37–38 months, one died of recurrent disease of the first carcinoma 36 months later, and one died of distant metastases of the second carcinoma 8 months later. There have been no local recurrences after treatments for the second primaries.

**Conclusions:** A variety of low-trauma treatments were employed for the second carcinomas because they were found at an early stage. Endoscopic follow-up is proposed to detect second lesions at an early stage.

*J. Surg. Oncol. 1997;66:130–133.* 

KEY WORDS: **esophageal carcinoma; residual esophageal carcinoma; second primary lesion; endoscopic mucosectomy; surgical mucosectomy; laser**

## INTRODUCTION

Esophageal carcinoma has a poor prognosis, with mean 2-year and 5-year survival rates after surgery of 34% and 20%, respectively [1]. Development of second primary carcinomas after esophagectomy has, therefore, previously been of little concern. However, recent reports show evident improvement in overall surgical 5-year survival rates, reaching 30% after esophagectomy with extended lymph node dissection [2,3]. Patients with squamous cell esophageal carcinoma are generally old, are smokers and alcohol drinkers, and they have a high risk of developing other tumors such as head and neck cancer [4]. In the procedure of subtotal esophagectomy,

Contract grant sponsor: Grant-in-Aid for Cancer Research Ministry of Health and Welfare of Japan; Contract grant number: 6–32.

*Correspondence to: Hoichi Kato, M.D., National Cancer Center Hospital, 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104, Japan. Fax: (81)3-3542-3815.

Accepted 23 June 1997

**TABLE I. Clinicopathological Features of the First Carcinoma of the Thoracic Esophagus**

| Case | Age | Sex | Location | pTNM stage | Histology | Proximal margin | Vascular invasion | Dysplasia | Others |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 55 | male | Middle | pT2N0M0 | mod.diff. scc.[a] | 41mm | Negative | Positive | — |
| 2 | 49 | male | Lower | pT3N0M0 | mod.diff. scc. | 55mm | Negative | Positive | Pharyngeal ca.[b] |
| 3 | 63 | male | Middle | pT3N0M0 | mod.diff. scc. | 55mm | Positive | Positive | — |
| 4 | 57 | male | Middle | pT1N0M0 | mod.diff. scc. | 125mm | Negative | Positive | Gastric ca. |
| 5 | 56 | male | Upper | pT1N1M0 | mod.diff. scc. | 35mm | Positive | Positive | Postgastrectomy |
| | | | Middle | | mod.diff. scc. | | | | (Duodenal ulcer) |

[a]mod. diff. scc., moderately differentiated squamous cell carcinoma.
[b]ca., carcinoma.

a small segment of the proximal esophagus is left to form the anastomosis with the substitution. There is, therefore, a risk of developing a second neoplasm in the proximal remnant in patients who have survived the first esophageal carcinoma.

This article reports our experience of diagnosing and treating second primary esophageal carcinomas arising in the remaining esophagus after thoracic esophagectomy.

## PATIENTS

From 1985 through 1994, 600 patients underwent esophagectomy for thoracic esophageal carcinoma in our institute, of whom 253 (42.2%) lived more than 2 years. There were 221 men and 32 women, with an average age of 62.1 years. Among these 253 patients, 5 (2.0%) were subsequently found to have second primary carcinomas in the remaining cervical esophagus.

## REPORT OF FIVE CASES

### First Esophageal Carcinoma

The clinicopathologic features of the first esophageal carcinoma of the five patients are shown in Table I. All five patients were male, and the average age at thoracic esophagectomy was 56.8 years. The esophagectomies were performed through thoracotomy and laparotomy. Four underwent cervical, mediastinal, and abdominal lymph node dissection, and another underwent mediastinal and abdominal dissection [5]. All esophagectomies were curative with tumor-free surgical margins and without residual tumor. Three patients underwent esophageal reconstruction through a retrosternal route using a tubed stomach. In the remaining two patients, the colon was used because of simultaneous gastric carcinoma or because of previous gastrectomy for benign duodenal ulcer.

Histological examination of the resected specimens revealed that all surgical margins were free of tumor, although there was scattered dysplastic mucosa around the carcinomas. Carcinoma invading the proper muscle of the esophagus (stage pT2) occurred in three patients. The remaining two patients had carcinoma invading to the submucosa (stage pT1), of whom case 5 was found to have two carcinomas in the resected specimen, both of which had invaded to the submucosa. This case also had a lymph node metastasis around the recurrent nerve, which was excised together with the esophagus. The remaining four patients had no positive lymph nodes in the resected specimen.

Case 4 had two synchronous adenocarcinomas in the stomach at initial surgery, and case 2 had synchronous hypopharyngeal carcinoma. Both patients underwent curative excision of all these carcinomas during the first esophagectomy. No patients had received any treatment for the first carcinoma before surgery. Case 1 received postoperative adjuvant chemotherapy with cisplatinum (180 mg) and vindesine (8.8 mg).

### Second Primary Esophageal Carcinoma

The second primary esophageal carcinomas were all found during outpatient follow-up examinations. Their clinicopathologic features are shown in Table II. The earliest second primary lesion was detected 30 months after the first esophagectomy. All the second primary carcinomas were found by endoscopy in the remaining cervical esophagus without any symptoms. Esophagography was incompetent to describe the figure of the lesions even under the information of endoscopic findings. CT scan and US also could not demonstrate tumors. Endoscopically, all second lesions were superficial and depressed and were clinically diagnosed to be at stage Tis or T1 with epithelial extension. None had metastasized.

### Treatments and the Results for Second Carcinoma

Treatments for the second primaries are summarized in Table II. There were no complications. Because all the second lesions were limited within the submucosa, and four of the five patients had already received cervical lymph node dissection at the first esophagectomy, they underwent limited treatments for the second lesions. Our standard strategy for superficial esophageal carcinoma that we suspect has invaded the submucosa is surgical resection with lymphadenectomy, and for tumors without infiltration to the mucosal muscle layer the usual treatment is endoscopic mucosal resection (EMR). EMR is considered to be the treatment of choice for these super-

**TABLE II. Clinicopathologic Features of the Second Primary Carcinoma in the Residual Cervical Esophagus**

| Case | Interval after first therapy | Endoscopic appearance | T/pT-stage | Histology | Treatment | Outcone |
|---|---|---|---|---|---|---|
| 1 | 7 year 5 months | Superficial depressed | T1/— | scc. (biopsy)[a] | Laser irradiation (Nd: YAG laser) | alive without disease 3 year 2 months |
| 2 | 5 year 1 month | Superficial depressed | Tis/pTis | scc. in situ | Surgical mucosectomy | alive without disease 3 years 1 month |
| 3 | 3 years 7 months | Superficial depressed | T1/pT1 | mod. diff. scc. | Surgical mucosectomy | death 3 years |
| 4 | 4 years 9 months | Superficial depressed | T1/pT1 | por. diff. scc. | Segmental resection | death 8 years |
| 5 | 2 years 6 months | Superficial depressed | T1/pT1 | well diff. scc. | Endoscopic mucosectomy | alive without disease 3 years 2 months |

[a]scc., squamous cell carcinoma; mod., moderately; diff., differentiated; por., poorly.

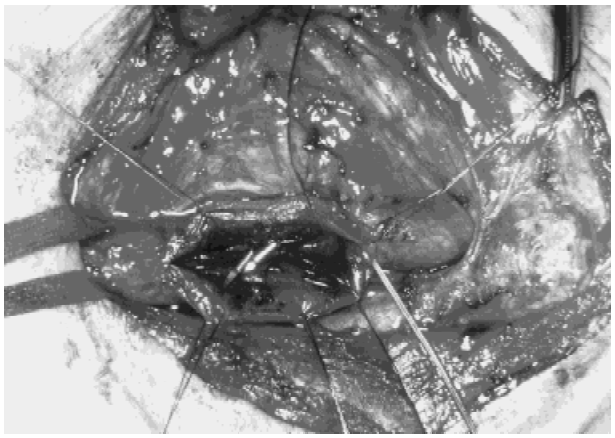

Fig. 1. Operative photograph of the second primary carcinoma in case 2. Through an esophagotomy wound unfolded by several staysutures, vital staining of the mucosa using Lugol solution shows an unstained lesion in the cervical esophagus. Two clips have been placed endoscopically on the distal edge of the tumor prior to surgery to indicate the location of the lesion.

ficial lesions, because the size of the tumor and the depth of invasion can be characterized, and because it is a low-trauma procedure for the patient. This method, however, was used only in case 5 because of technical problems. Case 1 was treated with Nd: YAG laser irradiation, because endoscopic mucosal resection was impossible on account of the tumor location close to the anastomosis site. Two patients underwent surgical mucosectomy via a cervical esophagotomy, because in case 2 the lesion was close to the esophageal orifice, and in case 3 close to the anastomosis, precluding complete resections by endoscopy. Combination of endoscopy and the Lugol staining method were valuable intraoperative methods for tumor location [6] (Fig. 1). In case 4 the tumor was suspected on endoscopy to have invaded the submucosa, and the procedure adopted was segmental resection of the cervical esophagus together with a part of the colon that had been anastomosed as a substitution for the thoracic esophagus. The scar and connective tissue around the esophagus were cautiously dissected with the esophagus. The digestive tract reconnection was established by an end-to-end anastomosis.

Three patients were alive without disease in March 1997. One patient (case 3) died of an anastomotic recurrence supposedly of lymphatic infiltration of the primary carcinoma, and another patient (case 4) died of hematogenous recurrence of the second carcinoma (a poorly differentiated squamous cell carcinoma that had widely invaded the submucosal layer). There were no cases of local recurrence after treatment of the second carcinoma.

## DISCUSSION

All the thoracic esophagi excised during primary surgery had tumor-free proximal surgical margins. Although more than 2½ years had elapsed after esophagectomies for the first lesions, all the second lesions in the cervical esophagus were at a relatively early stage and had epithelial components. These findings indicated that the second lesions were primary lesions newly arising in the remaining esophagus.

It is not uncommon for patients with esophageal carcinoma to have multiple primary carcinomas in the stomach or head and neck regions [4,7,8], and we have reported that 18.8% of patients with thoracic esophageal carcinoma had multiple primary lesions in the esophagus [9]. Moreover, during the last decade, 42% of the patients with thoracic esophageal carcinoma have survived more than 2 years after surgery in our institute. It is therefore increasingly important to detect second primary esophageal lesions after thoracic esophagectomy, even though the potential extent of tissue in which new tumors can arise is very small. To detect second primary lesions at an early stage, the remaining cervical esophagus should be examined at least annually, and this is now our usual practice.

All the second lesions in this series were found at a relatively early stage using endoscopy. However, endoscopic examination of the patients was not technically easy because the remaining esophagus was very short and curved. Esophagography could not demonstrate the

precise configuration of the lesions, which was performed several days after endoscopy to investigate the anatomical location of the lesion in relation to the pharynx. Neither CT scan nor US could demonstrate tumors. Accordingly, follow-up examination with endoscopy in experienced hands may be the best choice for the upper digestive tract of patients after thoracic esophagectomy.

Lesser procedures such as photocoagulation laser irradiation, photodynamic therapy, or endoscopic mucosal resection may be the treatments of choice in patients with esophageal carcinoma at an early stage to reduce the physical and economical burden on patients [10]. Because all the second primary lesions in this series were found to be stage Tis or T1, these treatment modalities are appropriate. Endoscopic mucosal resection may be the best treatment of choice for these lesions, because the pT stage of the lesion and the completeness of the treatment can be confirmed in the endoscopically excised specimen. However, endoscopic treatment of the remaining esophagus was often difficult in patients after thoracic esophagectomy, because the lesions were naturally close to the pharynx and the cervical esophagus was distorted by the retrosternal or subcutaneous reconstruction performed during earlier surgery. In addition, if the tumor is located on the anterior wall of the cervical esophagus, endoscopic treatment is technically difficult. Nd: YAG laser irradiation was used in case 1, whose true pT stage cannot therefore be known definitively. Two other patients underwent surgical mucosectomy under general anesthesia. This is a limited operation, but technically simple, because the location of the lesion could be identified precisely during operation with a combination endoscopy and Lugol staining. Radiation therapy was not chosen because the significance of radiation therapy, including external or brachytherapy for superficial esophageal carcinoma, had not been established. In case 4 the tumor had invaded the submucosa, and segmental resection of the esophagus and regional lymph node dissection were performed in an attempt to eradicate lymphatic infiltration [11]. Although there was no recurrence in the neck in this case, distant metastases occurred in the liver and lung.

## CONCLUSIONS

Clinicians should be aware of the risk of second primary esophageal carcinomas arising in the residual esophagus after esophagectomy for thoracic esophageal carcinoma because recently the prognosis of thoracic esophageal carcinoma after esophagectomy with extended lymph node dissection has been improving. After thoracic esophagectomy, endoscopic examination may be the best method to detect it at an early stage. When a second lesion is found at an early stage, several kinds of limited treatment may be appropriate to reduce patient morbidity.

## REFERENCES

1. Muller JM, Erasmi H, Stelzner M, et al.: Surgical therapy of oesophageal carcinoma. Br J Surg 1990;77:845–857.
2. Isono K, Sato H, Nakayama K: Results of a nationwide study on the three-field lymph node dissection of esophageal carcinoma. Oncology 1991;48:441–420.
3. Lerut T, De Leyn P, Coosemans W, et al.: Surgical strategies in esophageal carcinoma with emphasis on radical lymphadenectomy. Ann Surg 1992;216:583–590.
4. Tachimori Y, Watanabe H, Kato H, et al.: Treatment for synchronous and metachronous carcinomas of the head and neck and esophagus. J Surg Oncol 1990;45:43–45.
5. Kato H, Watanabe H, Tachimori Y, Iizuka T: Evaluation of neck lymph node dissection for thoracic esophageal carcinoma. Ann Thorac Surg 1991;51:931–935.
6. Sugimachi K, Tsutsui S, Kitamura K, et al.: Lugol stain for intraoperative determination of the proximal surgical margin of the esophagus. J Surg Oncol 1991;46:226–229.
7. Nakayama K, Abo S: Concurrent cancer of the esophagus in Japan. Int Adv Oncol 1979;2:243–249.
8. Kato H, Tachimori Y, Watanabe H, et al.: Esophageal carcinoma simultaneously associated with gastric carcinoma: Analysis of clinicopathologic features and treatment. J Surg Oncol 1994;56: 122–127.
9. Mizobuchi S, Kato H, Tachimori Y, et al.: Multiple primary carcinoma of the esophagus. Surg Oncol 1993;2:249–253.
10. Kato H, Tachimori Y, Mizobuchi S, et al.: Cervical, mediastinal, and abdominal lymph node dissection (three-field dissection) for superficial carcinoma of the thoracic esophagus. Cancer 1993;72: 2879–2882.
11. Kato H, Tachimori Y, Watanabe H, et al.: Superficial esophageal carcinoma. Surgical treatment and the results. Cancer 1990;66: 2319–2323.